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Daily iron and folic acid supplementation in pregnant women

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Contents

	Acknowledgements	iv
	Financial support	iv
	Summary	1
	Scope and purpose	2
	Background	2
	Summary of evidence	3
	Recommendation	4
	Remarks	5
	Implications for future research	6
	Dissemination, adaptation and implementation	6
	Dissemination	
	Adaptation and implementation	
	Monitoring and evaluation of guideline implementation	
	Guideline development process	7
	Advisory groups	
	Scope of the guideline, evidence appraisal and decision-making	
	Management of conflicts of interest	10
	Plans for updating the guideline	10
	References	11
Annex 1	GRADE "Summary of findings" tables	13
Annex 2	Summary of the considerations by the Nutrition Guidance Expert Advisory Group for determining the strength of the recommendation	17
Annex 3	WHO Steering Committee for Nutrition Guidelines Development	18
Annex 4	Nutrition Guidance Expert Advisory Group – Micronutrients, WHO Secretariat and external resource experts	19
Annex 5	External Experts and Stakeholders Panel – Micronutrients	23
Annex 6	Questions in Population, Intervention, Control, Outcomes (PICO) format	27

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WHO Guideline[1] Daily iron and folic acid supplementation in pregnant women

Summary

It is estimated that 41.8% of pregnant women worldwide are anaemic. At least half of this anaemia burden is assumed to be due to iron deficiency. Member States have requested guidance from the World Health Organization (WHO) on the effectiveness and safety of daily iron and folic acid supplementation in pregnant women as a public health measure to improve pregnancy outcomes in support of their efforts to achieve the Millennium Development Goals.

WHO developed the present evidence-informed recommendations using the procedures outlined in the *WHO handbook for guideline development*. The steps in this process included: (i) identification of priority questions and outcomes; (ii) retrieval of the evidence; (iii) assessment and synthesis of the evidence; (iv) formulation of recommendations, including research priorities; and (v) planning for dissemination, implementation, impact evaluation and updating of the guideline. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was followed to prepare evidence profiles related to preselected topics, based on up-to-date systematic reviews.

The guideline advisory group for nutrition interventions, the Nutrition Guidance Expert Advisory Group, comprises content experts, methodologists, representatives of potential stakeholders and consumers. These experts participated in several WHO technical consultations concerning this guideline, held in Geneva, Switzerland, and in Amman, Jordan, in 2010 and 2011. Members of the External Experts and Stakeholders Panel were identified through a public call for comments, and this panel was involved throughout the guideline development process. Guideline advisory group members voted on the strength of the recommendation, taking into consideration: (i) desirable and undesirable effects of this intervention; (ii) the quality of the available evidence; (iii) values and preferences related to the intervention in different settings; and (iv) the cost of options available to health-care workers in different settings. All the members of the guideline advisory group completed a Declaration of Interests Form before each meeting.

Daily oral iron and folic acid supplementation is recommended as part of the antenatal care to reduce the risk of low birth weight, maternal anaemia and iron deficiency (*strong recommendation*). The overall quality of the evidence for iron supplementation versus no iron was moderate for low birth weight, preterm birth, maternal anaemia at term and maternal iron deficiency at term. The evidence was of low quality for birth weight, neonatal death, congenital anomalies, maternal death, maternal severe anaemia, and infections during pregnancy; whereas it was of very low quality for side-effects.

[1]This publication is a WHO guideline. A WHO guideline is any document, whatever its title, containing WHO recommendations about health interventions, whether they be clinical, public health or policy interventions. A recommendation provides information about what policy-makers, health-care providers or patients should do. It implies a choice between different interventions that have an impact on health and that have ramifications for the use of resources. All publications containing WHO recommendations are approved by the WHO Guidelines Review Committee.

Scope and purpose

This guideline provides global, evidence-informed recommendations on daily iron and folic acid supplementation as a public health intervention for the purpose of improving pregnancy outcomes and reducing maternal anaemia in pregnancy.

The guideline will help Members States and their partners in their efforts to make informed decisions on the appropriate nutrition actions to achieve the Millennium Development Goals, in particular, reduction of child mortality (MDG 4) and improvement in maternal health (MDG 5). The guideline is intended for a wide audience including policy-makers, their expert advisers, and technical and programme staff at organizations involved in the design, implementation and scaling-up of nutrition actions for public health.

This document presents the key recommendation and a summary of the supporting evidence. Further details of the evidence base are provided in Annex 1 and other documents listed in the references.

Background

It is estimated that 41.8% of pregnant women worldwide are anaemic (*1*). At least half of this burden is assumed to be due to iron deficiency (*2*), with the rest due to conditions such as folate, vitamin B_{12} or vitamin A deficiency, chronic inflammation, parasitic infections and inherited disorders. A pregnant woman is considered to be anaemic if her haemoglobin concentration during the first and third trimester of gestation is lower than 110 g/L, at sea level; in the second trimester of pregnancy, the haemoglobin concentration usually decreases by approximately 5 g/L (*3*). When anaemia is accompanied by an indication of iron deficiency (e.g. low ferritin levels), it is referred as iron deficiency anaemia (*2*).

Low haemoglobin concentrations indicative of moderate or severe anaemia during pregnancy have been associated with an increased risk of premature delivery, maternal and child mortality, and infectious diseases (*4*). Iron deficiency anaemia may affect growth and development both in utero (*2*) and in the long term (*5*). Haemoglobin concentrations greater than 130 g/L at sea level may also be associated with negative pregnancy outcomes such as premature delivery and low birth weight (*6, 7*).

Interventions aimed at preventing iron deficiency and iron deficiency anaemia in pregnancy include iron supplementation, fortification of staple foods with iron, health and nutrition education, control of parasitic infections, and improvement in sanitation (*8*). Delayed umbilical cord clamping is also effective in preventing iron deficiency among infants and young children (*9*). During pregnancy, women need to consume additional iron to ensure they have sufficient iron stores to prevent iron deficiency (*10*). Therefore, in most low- and middle-income countries, iron supplements are used extensively by pregnant women to prevent and correct iron deficiency and anaemia during gestation.

A standard supplemental dose of 60 mg of elemental iron was first established in 1959, based on estimates of iron requirements in pregnant women (*11*); this dose has since been endorsed by several expert consultations (*4, 12, 13*). A prophylactic dose of 300 µg (0.3 mg) per day throughout pregnancy was suggested in 1968 by the World Health Organization (WHO). The supplemental dose was increased to 400 µg (0.4 mg) of folic acid per day in 1998 following publication of several studies supporting

the periconceptional use of this nutrient in the prevention of neural tube defects. This dose was deemed to provide more folic acid than required to produce an optimal haemoglobin response in pregnant women. If supplementation is started after the first trimester of pregnancy it will not help prevent birth defects (*13*).

Gastrointestinal distress is a common observation in women consuming large amounts of supplemental iron, particularly on an empty stomach. Thus gastrointestinal side-effects are considered as the critical adverse effect on which to base the tolerable upper level of intake for iron. Use of high-dose iron supplements is commonly associated with constipation and other gastrointestinal effects, including nausea, vomiting and diarrhoea, with the frequency and severity depending on the amount of elemental iron released in the stomach.

Summary of evidence

An existing Cochrane systematic review (*14*) assessing the benefits and harms of iron supplementation in healthy pregnant women was updated for this guideline. The updated review (*15*) compared the daily provision of iron supplements alone or in combination with folic acid or other micronutrients with no intervention, placebo or versus the use of the same supplements but without iron (e.g. only folic acid) among pregnant women living in a variety of settings, including malaria-endemic areas.

The infant outcomes ranked as critical for decision-making by the Nutrition Guidance Expert Advisory Group were low birth weight, weight at birth, prematurity, perinatal death and congenital anomalies, including neural tube defects. The maternal outcomes considered were anaemia, iron deficiency and iron deficiency anaemia at term, as well as the presence of any side-effects, clinical malaria or infections during pregnancy. The potential effects of baseline anaemia status, gestational age at the start of supplementation, malaria setting and the daily dose of iron were also evaluated.

The review included 60 randomized controlled trials with 27 402 women from 30 different countries in all continents. Only 43 trials contributed data to the review, albeit not all of them reported on all the outcomes; 16 of the trials were of high quality according to the pre-established criteria. Twenty-three studies were conducted in countries that in 2011 had some malaria risk in parts of the country. In some of these countries/territories, malaria is present only in certain areas or up to a particular altitude. Only two of these studies reported malaria outcomes. It was not always clear from the reports whether malaria prevention and control programmes were in place at the time when these studies were conducted or whether concomitant malaria interventions were made available to the study participants.

Overall, women taking daily iron supplements were less likely to have low birth weight babies compared with controls (average relative risk (RR) 0.81, 95% confidence interval (CI) 0.68 – 0.97, 11 studies) and the mean birth weight was 30.81g greater for those infants whose mothers received iron during pregnancy (95% CI 5.94 – 55.68 g, 14 studies). There was no significant effect on preterm birth or neonatal death.

Daily iron supplementation reduced the risk of maternal anaemia at term by 70% (RR 0.30, 95% CI 0.19 – 0.46, 14 trials) and iron deficiency at term by 57% (RR 0.43, 95% CI 0.27 – 0.66, seven studies), but it had no significant effect on the risk of infections during pregnancy (RR 1.16, 95% CI 0.83 – 1.63, two studies). Women receiving iron had 8.88 g more haemoglobin per litre at or near term (95% CI 6.96 – 10.80, 19 studies) than those who did not receive iron. At the same time, women who received iron supplements tended to report more frequently side-effects (RR 2.36, 95% CI 0.96 to 5.82, 11 studies) and were at increased risk of high haemoglobin concentrations (i.e. greater than 130 mg/L) during the second and third trimesters of pregnancy (RR 2.26, 95% CI 1.40 – 3.66, 10 studies).

The intervention seems to be effective among populations with different prevalences of anaemia, and in settings described as malaria-endemic, when compared with settings where malaria is sporadic or absent, and regardless of whether the supplementation was initiated earlier or later than 20 weeks of gestation or whether the daily dose of elemental iron was 30 mg or less, 31–59 mg, or 60 mg or higher. However, women receiving 60 mg of iron or more were more likely to have haemoglobin concentrations above 130 g/L and report side effects (RR 6.52, 95% CI 1.13, 37.69) than dose women receiving 30 mg per day or less (RR 1.01, 95% CI 0.84 – 1.21).

The overall quality of the evidence for iron supplementation versus no iron was moderate for low birth weight, preterm birth, maternal anaemia at term and maternal iron deficiency at term. The evidence was of low quality for birth weight, neonatal death, congenital anomalies, maternal death, maternal severe anaemia, and infections during pregnancy; whereas it was of very low quality for side-effects (Annex 1).

Recommendation

This guideline updates the WHO recommendations published previously (*2*).

Daily oral iron and folic acid supplementation is recommended as part of the antenatal care to reduce the risk of low birth weight, maternal anaemia and iron deficiency (*strong recommendation*)[1, 2].

A suggested scheme for daily iron and folic acid supplementation in pregnant women is presented in Table 1.

[1] A strong recommendation is one for which the guideline development group is confident that the desirable effects of adherence outweigh the undesirable effects. The recommendation can be either in favour of or against an intervention. Implications of a strong recommendation for patients are that most people in their situation would desire the recommended course of action and only a small proportion would not. For clinicians, the implications are that most patients should receive the recommended course of action, and adherence to this recommendation is a reasonable measure of good-quality care. With regard to policy-makers, a strong recommendation means that it can be adapted as a policy in most situations.

[2] Considerations of the guideline advisory group for determining the strength of the recommendation are summarized in Annex 2.

Table 1

Suggested scheme for daily iron and folic acid supplementation in pregnant women

Supplement composition	Iron: 30–60 mg of elemental iron[a] Folic acid: 400 µg (0.4 mg)
Frequency	One supplement daily
Duration	Throughout pregnancy. Iron and folic acid supplementation should begin as early as possible
Target group	All pregnant adolescents and adult women
Settings	All settings

[a] 30 mg of elemental iron equals 150 mg of ferrous sulfate heptahydrate, 90 mg of ferrous fumarate or 250 mg of ferrous gluconate.

Remarks

- In settings where anaemia in pregnant women is a severe public health problem (40% of higher), a daily dose of 60 mg of elemental iron is preferred over a lower dose.
- If a woman is diagnosed with anaemia in a clinical setting, she should be treated with daily iron (120 mg of elemental iron) and folic acid (400 µg or 0.4 mg) supplementation until her haemoglobin concentration rises to normal (*2, 21*). She can then switch to the standard antenatal dose to prevent recurrence of anaemia.
- Folic acid requirements are increased in pregnancy because of the rapidly dividing cells in the fetus and elevated urinary losses. As the neural tube closes by day 28 of pregnancy, when pregnancy may not have been detected, folic acid supplementation after the first month of pregnancy will not prevent neural tube defects. However, it will contribute to other aspects of maternal and fetal health. Give iron supplements even if folic acid is not available.
- In addition to iron and folic acid, supplements may be formulated to include other vitamin and minerals according to the United Nations Multiple Micronutrient Preparation (*16*) to overcome other possible maternal micronutrient deficiencies.
- In malaria-endemic areas, provision of iron and folic acid supplements should be implemented in conjunction with measures to prevent, diagnose and treat malaria (*17–19*).

- An iron and folic acid supplementation programme should ideally form part of an integrated programme of antenatal and neonatal care (*20, 21*) that promotes adequate gestational weight gain, screening of all women for anaemia at antenatal and postpartum visits, use of complementary measures to control and prevent anaemia (e.g. hookworm control), and a referral system to manage cases of severe anaemia.

- The implementation of a behaviour change communication strategy to communicate the benefits of the intervention and management of side-effects, along with provision of supplements of good quality and appropriate packaging, is vital to improving the acceptability of and adherence to recommended supplementation schemes. The strategy can also serve to promote the use of dietary diversity and intake of food combinations that improve iron absorption.

- Oral supplements are available as capsules or tablets (soluble, tablets, dissolvable and modified-release tablets) (*22*). Establishment of a quality assurance process is important to guarantee that supplements are manufactured, packaged and stored in a controlled and uncontaminated environment (*23*).

Implications for future research

Discussion with the guideline development group and stakeholders highlighted the limited evidence available in some areas, meriting further research on daily iron and folic acid supplementation in pregnant women, in particular, in the following areas:

- effects of supplementation of vitamins and other minerals in addition to iron and folic acid on maternal and neonatal outcomes;

- side-effects, as they are often poorly defined and reported (e.g. there is no information on intensity or frequency of most side-effects);

- operational issues related to improving delivery and utilization of this intervention;

- effects of this intervention on fetal growth and programming of chronic diseases.

Dissemination, adaptation and implementation

Dissemination

The current guideline will be disseminated through electronic media such as slide presentations, CD-ROMs and the World Wide Web, either through or the WHO nutrition web site, the WHO Micronutrients and United Nations Standing Committee on Nutrition (SCN) mailing lists, or the WHO e-Library of Evidence for Nutrition Actions (eLENA). This library aims to compile and display WHO guidelines related to nutrition, along with complementary documents such as systematic reviews and other evidence that informed the guidelines, biological and behavioural rationales, and additional resources produced by Member States and global partners. The guideline

will also be disseminated through a broad network of international partners, including WHO country and regional offices, ministries of health, WHO collaborating centres, universities, other United Nations agencies and nongovernmental organizations. It will also be published in the WHO Reproductive Health Library.

Adaptation and implementation

As this is a global guideline it should be adapted to the context of each Member State. Prior to implementation, an iron supplementation programme should have well-defined objectives that take into account available resources, existing policies, suitable delivery platforms and suppliers, communication channels, and potential stakeholders. Ideally, iron and folic acid supplementation should be implemented as part of an integrated programme for antenatal and neonatal care.

To ensure that WHO global guidelines and other evidence-informed recommendations for micronutrient interventions are better implemented in low- and middle-income countries, the Department of Nutrition for Health and Development works with the WHO Evidence-Informed Policy Network (EVIPNet) programme. EVIPNet promotes partnerships at country level between policy-makers, researchers and civil society to facilitate policy development and implementation through use of the best available evidence.

Monitoring and evaluation of guideline implementation

A plan for monitoring and evaluation with appropriate indicators is encouraged at all stages. The impact of this guideline can be evaluated within countries (i.e. monitoring and evaluation of the programmes implemented at large scale) and across countries (i.e. the adoption and adaptation of the guideline globally). The WHO Department of Nutrition for Health and Development, jointly with the Centers for Disease Control and Prevention (CDC) International Micronutrient Malnutrition Prevention and Control (IMMPaCt) programme, and with input from international partners, has developed a generic logic model for micronutrient interventions in public health to depict the plausible relationships between inputs and expected MDGs by applying the micronutrient programme evaluation theory. Member States can adjust the model and use it in combination with appropriate indicators for designing, implementing, monitoring and evaluating the successful scaling-up of nutrition actions (*24*).

For evaluation at the global level, the WHO Department of Nutrition for Health and Development is developing a centralized platform for sharing information on nutrition actions in public health practice implemented around the world. By sharing programmatic details, specific country adaptations and lessons learnt, this platform will provide examples of how guidelines are being translated into nutrition actions.

Guideline development process

This guideline was developed in accordance with the WHO evidence-informed guideline development procedures, as outlined in the *WHO handbook for guideline development* (*25*).

Advisory groups

The WHO Steering Committee for Nutrition Guidelines Development, led by the Department of Nutrition for Health and Development and the Department of Research Policy and Cooperation, was established in 2009 with representatives from all WHO departments with an interest in the provision of scientific nutrition advice, including Child and Adolescent Health and Development, Reproductive Health and Research, and the Global Malaria Programme. The Steering Committee guided the development of this guideline and provided overall supervision of the guideline development process (Annex 3). Two additional groups were formed: an advisory guideline group and an External Experts and Stakeholders Panel.

The Nutrition Guidance Expert Advisory Group, was established in 2009 (Annex 4). It has four subgroups: (i) Micronutrients, (ii) Diet and Health, (iii) Nutrition in Life course and Undernutrition, and (iv) Monitoring and Evaluation. Its role is to advise WHO on the choice of important outcomes for decision-making and in the interpretation of the evidence. The group includes experts from various WHO expert advisory panels and those identified through open calls for specialists, taking into consideration a balanced gender mix, multiple disciplinary areas of expertise and representation from all WHO regions. Efforts were made to include content experts, methodologists, representatives of potential stakeholders (such as managers and other health professionals involved in the health-care process) and consumers. Representatives of commercial organizations may not be members of a WHO guideline group.

The External Experts and Stakeholders Panel was consulted on the scope of the guideline, the questions addressed, and the choice of important outcomes for decision-making, as well as with regard to review of the completed draft guideline (Annex 5). This was done through the WHO Micronutrients and SCN mailing lists that together include over 5500 subscribers, and through the WHO nutrition web site.

Scope of the guideline, evidence appraisal and decision-making

An initial set of questions (and the components of the questions) to be addressed in the guideline was the critical starting point for formulating the recommendation; the questions were drafted by technical staff at the Micronutrients Unit, Department of Nutrition for Health and Development, based on policy and programme guidance needs of Member States and their partners. The population, intervention, control, outcomes (PICO) format was used (Annex 6). The questions were discussed and reviewed by the Steering Committee and feedback was received from 48 stakeholders.

The first meeting with the Nutrition Guidance Expert Advisory Group was held on 22–26 February 2010 in Geneva, Switzerland, to finalize the scope of the questions and rank the critical outcomes and populations of interest. The nutrition guideline expert advisory group – Micronutrients Subgroup discussed the relevance of the questions and modified them as needed. The guideline group members scored the relative importance of each outcome from 1 to 9 (where 7–9 indicated that the outcome was critical for a decision, 4–6 indicated that it was important and 1–3 indicated that it was not important). The final key questions on iron and folic acid supplementation in pregnant women, along with the outcomes that were identified as critical for decision-making are listed in PICO format in Annex 6.

WHO staff, in collaboration with researchers from other institutions, summarized and appraised the evidence using the Cochrane methodology for randomized controlled trials[1]. For identifying unpublished studies or studies still in progress, a standard procedure was followed to contact more than 10 international organizations working on micronutrient interventions. In addition, the International Clinical Trials Registry Platform (ICTRP), hosted at WHO, was systematically searched for any trials still in progress. No language restrictions were applied in the search. Evidence summaries were prepared according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the overall quality of the evidence (*26*). GRADE considers: the study design; the limitations of the studies in terms of their conduct and analysis; the consistency of the results across the available studies; the directness (or applicability and external validity) of the evidence with respect to the populations, interventions and settings where the proposed intervention may be used; and the precision of the summary estimate of the effect.

Both the systematic review and the GRADE evidence profiles for each of the critical outcomes were used for drafting this guideline. The draft recommendation was reviewed by the WHO Nutrition Guidance Steering Committee and the Nutrition Guidance Expert Advisory Group members at a second consultation, held on 15–18 November 2010 in Amman, Jordan, and at the third consultation, held on 14–16 March 2011 in Geneva, Switzerland, where the guideline development group members also voted on the strength of the recommendation, taking into account: (i) desirable and undesirable effects of this intervention; (ii) the quality of the available evidence; (iii) values and preferences related to the intervention in different settings; and (iv) the cost of options available to health-care workers in different settings (Annex 2). Consensus was defined as agreement by simple majority of guideline group members. WHO staff present at the meeting as well as other external technical experts involved in the collection and grading of the evidence were not allowed to vote. There were no strong disagreements among the guideline group members.

A public call for comments on the final draft guideline was then released. All interested stakeholders became members of the External Experts and Stakeholders Panel but were only allowed to comment on the draft guideline after submitting a signed Declaration of Interests Form. Feedback was received from 15 stakeholders. WHO staff then finalized the guideline and submitted it for clearance by WHO before publication.

[1] As part of the Cochrane pre-publication editorial process, this review was commented on by three external peers (an editor, and two referees who are external to the editorial team) and the group's statistical adviser (http://www.cochrane.org/cochrane-reviews). The *Cochrane handbook for systematic reviews of interventions* describes in detail the process of preparing and maintaining Cochrane systematic reviews on the effects of health-care interventions.

Management of conflicts of interest

According to the rules in the WHO *Basic documents* (*27*), all experts participating in WHO meetings must declare any interest relevant to the meeting prior to their participation. The conflicts of interest statements for all guideline group members were reviewed by the responsible technical officer and the relevant departments before finalization of the group composition and invitation to attend a guideline group meeting. All guideline group members and participants of the guideline development meetings submitted a Declaration of Interests Form along with their curriculum vitae before each meeting. In addition, they verbally declared potential conflicts of interest at the beginning of each meeting. The procedures for management of conflicts of interests strictly followed WHO *Guidelines for declaration of interests (WHO experts)* (*28*). The potential conflicts of interest declared by the members of the guideline group are summarized below.

- Dr Héctor Bourges Rodriguez declared being chair of the executive board of the Dannon Institute in Mexico (DIM), a non-profit organization promoting research and dissemination of scientific knowledge in nutrition, and receiving funds as chair honorarium from DIM. Some of the activities of the DIM may generally relate to nutrition and are funded by Danone Mexico, a food producer.

- Dr Norm Campbell at the first meeting declared owning stock in Viterra, a wheat pool for farmers that neither manufactures products nor undertakes activities related to this guideline. In 2011, Dr Campbell declared no longer owning stocks in this company. He serves as a Pan American Health Organization (PAHO) consultant and has been an adviser to Health Canada and Blood Pressure Canada, both of which are government agencies.

- Dr Emorn Wasantwisut declared serving as a technical/scientific adviser to the International Life Sciences Institute (ILSI)/South East Asia's Food and Nutrients in Health and Disease Cluster and as a reviewer of technical documents and speaker for Mead Johnson Nutritionals. Her research unit received funds for research support from Sight and Life and the International Atomic Energy Agency (IAEA) for the use of stable isotopes to define interactions of vitamin A and iron.

- Dr Beverley Biggs declared that the University of Melbourne received funding from the National Health and Medical Research Council (NHMRC) and the Australian Research Council (ARC) for research on weekly iron and folic acid supplementation in pregnancy, conducted in collaboration with the Research and Training Center for Community Development (RTCCD), the Key Centre for Women's Health and the Murdoch Childrens Research Institute.

Plans for updating the guideline

This guideline will be reviewed in 2016. If new information is available at that time, a guideline review group will be convened to evaluate the new evidence and revise the recommendation if needed. The Department of Nutrition for Health and Development at the WHO headquarters in Geneva, along with its internal partners, will be responsible for coordinating the guideline update, following formal *WHO handbook for guideline development* (*25*) procedures. WHO welcomes suggestions regarding additional questions for evaluation in the guideline when it is due for review.

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Annex 1 GRADE "Summary of findings" tables

Any supplements containing iron versus same supplements without iron, no treatment or placebo for pregnant women

Patient or population: Pregnant women

Settings: All settings including malaria-endemic areas

Intervention: Any supplements containing iron versus no treatment/placebo or the same supplements without iron

Outcomes	Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)*	Comments
Low birth weight (less than 2500 g)	**RR 0.81** (0.68 – 0.97)	8 480 (11 studies)	⊕⊕⊕⊖ **moderate**[1]	
Birth weight (g)	The mean difference (g) between groups was 30.81 (5.94 – 55.68)	9 385 (14 studies)	⊕⊕⊖⊖ **low**[2]	
Preterm birth (less than 37 weeks of gestation)	**RR 0.88** (0.77 – 1.01)	10 148 (13 studies)	⊕⊕⊕⊖ **moderate**[3]	
Neonatal death (within 28 days after birth)	**RR 0.90** (0.68 – 1.19)	7 465 (4 studies)	⊕⊕⊖⊖ **low**[4]	
Congenital anomalies	**RR 0.86** (0.55 – 1.35)	2 702 (3 studies)	⊕⊕⊖⊖ **low**[5]	

CI: confidence interval; **RR**: average risk ratio; **Hb**: haemoglobin.

*GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[1] Some of the trials contributing data had high levels of attrition and in several studies the method of allocation concealment was unclear. Low heterogeneity (16%). No serious imprecision.
[2] Some of the trials contributing data had high levels of attrition and in several studies the method of allocation concealment was unclear. There was no serious heterogeneity in the magnitude of the effect (23%) and most of the trials favoured iron supplementation. Wide confidence intervals.
[3] Some of the trials contributing data had high levels of attrition and in several studies the method of allocation concealment was unclear. Nil heterogeneity (0%). No serious imprecision.
[4] Some of the trials contributing data had high levels of attrition or the method of allocation concealment was unclear. Event rates in some trials were low and the 95% CI was very wide in these trials. Nil heterogeneity (0%). Some imprecision.
[5] No serious risk of bias in the trials contributing data. Event rates in one study were low and the confidence intervals were wide. Nil heterogeneity (0%). Some imprecision.

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Any supplements containing iron versus same supplements without iron, no treatment or placebo for pregnant women

Patient or population: Pregnant women

Settings: All settings including malaria-endemic areas

Intervention: Any supplements containing iron versus no treatment/placebo or the same supplements without iron

Outcomes	Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)*	Comments
Maternal anaemia at term (Hb less than 110 g/L at 37 weeks gestation or more)	**RR 0.30** (0.19 – 0.46)	2 199 (14 studies)	⨁⨁⨁⨀ **moderate**[6]	
Maternal iron deficiency at term (as defined by trialists, based on any indicator of iron status at 37 weeks' gestation or more)	**RR 0.43** (0.27 – 0.66)	1 256 (7 studies)	⨁⨁⨁⨀ **moderate**[7]	
Maternal death (death while pregnant or within 42 days of termination of pregnancy)	Not estimable	47 (1 study)	⨁⨁⨀⨀ **low**[8]	
Side-effects (any reported throughout the intervention period)	**RR 2.36** (0.96 – 5.82)	4 418 (11 studies)	⨁⨀⨀⨀ **very low**[9]	
Maternal severe anaemia at any time during 2nd or 3rd trimester (Hb less than 70 g/L)	**RR 0.22** (0.01 – 3.20)	2 125 (9 studies)	⨁⨁⨀⨀ **low**[10]	
Infection during pregnancy (including urinary tract infections and others)	**RR 1.16** (0.83 – 1.63)	3 421 (2 studies)	⨁⨁⨁⨀ **low**[11]	

CI: confidence interval; **RR**: average risk ratio; **Hb**: haemoglobin.

*GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[6] Some of the trials contributing data had high levels of attrition and in various studies the method of allocation concealment was unclear. Although the direction of the effect was the same in all these trials, the effect size varied considerably resulting in high heterogeneity (80%). No serious imprecision. Assessors refrained from downgrading due to the high magnitude of the effect.
[7] Some of the trials contributing data had high levels of attrition and in various studies the method of allocation concealment was unclear. Although the direction of the effect was the same in all these trials, the effect size varied considerably resulting in high heterogeneity (85%). No serious imprecision. Assessors refrained from downgrading due to the high magnitude of the effect.
[8] A single high quality trial assessed this outcome reporting zero events for both study arms.
[9] Some of the trials contributing data had high levels of attrition and in various studies the method of allocation concealment was unclear. There was serious heterogeneity in the magnitude of the effect (96%) but most of the trials favoured no intervention/placebo. Wide confidence intervals.
[10] Some of the trials contributing data had high levels of attrition and in various studies the method of allocation concealment was unclear. Nil heterogeneity (0%). Wide confidence intervals.
[11] Some of the trials contributing data had high levels of attrition and in various studies the method of allocation concealment was unclear. Nil heterogeneity (0%). Event rates in both studies were low and the confidence intervals were wide.

For details of studies included in the review, see reference (*15*).

Any supplements containing iron and folic acid versus same supplements without iron and folic acid, no treatment or placebo for pregnant women

Patient or population: Pregnant women

Settings: All settings including malaria-endemic areas

Intervention: Any supplements containing iron versus no treatment/placebo or the same supplements without iron and folic acid

Outcomes	Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)*	Comments
Low birthweight (less than 2500 g)	**RR 1.07** (0.31 – 3.74)	1 311 (2 studies)	⨁⊖⊖⊖ **very low**[1]	
Birth weight (g)	The mean difference (g) between the groups was 57.73 (7.66 –107.79)	1 365 (2 studies)	⨁⊖⊖⊖ **very low**[2]	
Preterm birth (less than 37 weeks of gestation)	**RR 1.55** (0.40 – 6.00)	1 497 (3 studies)	⨁⊖⊖⊖ **very low**[3]	
Neonatal death (within 28 days after birth)	**RR 0.81** (0.51 – 1.30)	1 793 (3 studies)	⨁⨁⊖⊖ **low**[4]	
Congenital anomalies	**RR 0.70** (0.35 – 1.40)	1 652 (1 study)	⨁⊖⊖⊖ **very low**[5]	

CI: confidence interval; **RR**: average risk ratio; **Hb**: haemoglobin.

*GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[1] One out of the two trials was considered at high risk of bias. Low heterogeneity (29%) but inconsistency in the magnitude and direction of the effect. Wide confidence intervals.
[2] One out of the two trials was considered at high risk of bias. Very low heterogeneity (2%) but inconsistency in the magnitude and direction of the effect. Wide confidence intervals.
[3] Two out of the three trials were considered at high risk of bias. Moderate heterogeneity (34%). Wide confidence intervals.
[4] Two of the three trials were considered at low risk of bias. Nil heterogeneity (0%). Wide confidence intervals.
[5] A single high-quality trial assessed this outcome, reporting low number of events for both study arms. Wide confidence intervals.

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Any supplements containing iron and folic acid versus same supplements without iron and folic acid, no treatment or placebo for pregnant women

Patient or population: Pregnant women

Settings: All settings including malaria-endemic areas

Intervention: Any supplements containing iron versus no treatment/placebo or the same supplements without iron and folic acid

Outcomes	Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)*	Comments
Maternal anaemia at term (Hb less than 110 g/L at 37 weeks gestation or more)	**RR 0.34** (0.21 – 0.54)	346 (3 studies)	⨁⨁⨁⨁ **high**[6]	
Maternal iron deficiency at term (as defined by trialists, based on any indicator of iron status at 37 weeks' gestation or more)	**RR 0.24** (0.06 – 0.99)	131 (1 study)	⨁⨁⨀⨀ **low**[7]	
Maternal death (death while pregnant or within 42 days of termination of pregnancy)	Not estimable	131 (1 study)	⨁⨁⨀⨀ **low**[8]	
Side-effects (any reported throughout the intervention period)	**RR 44.32** (2.77 – 709.09)	456 (1 study)	⨁⨁⨀⨀ **low**[9]	
Maternal severe anaemia at any time during 2nd or 3rd trimester (Hb less than 70 g/L)	**RR 0.12** (0.02 – 0.63)	506 (4 studies)	⨁⨁⨀⨀ **low**[10]	
Infection during pregnancy (including urinary tract infections and others)	**RR 1.00** (0.15 – 6.53)	48 (1 study)	⨁⨁⨀⨀ **low**[11]	

CI: confidence interval; **RR**: average risk ratio; **Hb**: haemoglobin.

*GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[6] Two out of three trials reported events and one was considered at high risk of bias. Nil heterogeneity (0%). No serious imprecision. Assessors refrained from downgrading due to the large magnitude of the effect.
[7] A single trial (at high risk of bias) assessed this outcome, reporting low number of events for both study arms. Wide confidence intervals. Assessors refrained from downgrading due to the large magnitude of the effect.
[8] A single trial (at high risk of bias) assessed this outcome reporting zero events for both study arms.
[9] A single high-quality trial assessed this outcome. Wide confidence intervals.
[10] Three out of four trials reported events and two were considered at high risk of bias. Nil heterogeneity (0%). Wide confidence intervals. Assessors refrained from downgrading due to the large magnitude of the effect.
[11] A single trial (at high risk of bias) assessed this outcome reporting low number of events for both study arms. Wide confidence intervals. Nil heterogeneity (0%). Event rates in both studies were low and the confidence intervals were wide.

For details of studies included in the review, see reference (*15*).

Annex 2 Summary of the considerations by the Nutrition Guidance Expert Advisory Group for determining the strength of the recommendation

Quality of evidence:	• The available evidence was considered sufficient and of adequate quality to support the recommendation in all settings
Values and preferences:	• Daily iron and folic acid supplementation in pregnancy helps prevent important health problems • In addition to maternal anaemia, daily iron supplementation has a positive effect on functional outcomes such as reducing the risk of low birth weight
Trade-off between benefits and harm:	• Benefits of this intervention far outweigh the harms
Cost and feasibility:	• It is perceived as an inexpensive intervention; it would be more cost-effective if countries implement it broadly • Issues related to adherence to the supplementation schedule may limit the implementation of this intervention

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Annex 6 Questions in Population, Intervention, Control, Outcomes (PICO) format

Effects and safety of daily iron and folic acid supplementation in pregnant women

a. Could daily iron and folic acid supplements be given to pregnant women to mprove maternal and infant health outcomes?

b. If so, at what dose, frequency and duration for the intervention, and in which settings?

Population:

- Subpopulation:

Critical

- By malaria-endemic versus non-malaria-endemic area (no transmission or elimination achieved; susceptibility to epidemic malaria; year-round transmission with marked seasonal fluctuations; year-round transmission with consideration of Plasmodium falciparum and/or Plasmodium vivax)
- By use of concurrent malarial measures, in particular intermittent preventive treatment in pregnancy (IPTp) with sulfadoxine-pyrimethamine (SP)
- By human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) status: HIV positive versus HIV negative
- By individual's status of iron deficiency: iron deficiency versus no iron deficiency
- By individual's status of anaemia: anaemia versus no anaemia
- By anaemia status of population: 20% or less versus 20–40% versus more than 40%

Intervention:

Daily oral iron plus folic acid supplementation

- Subgroup analysis:

Critical

- By start of supplementation: less than 20 20 weeks' gestation versus 20 weeks' gestation or later
- By nutrient: iron plus folic acid versus iron versus iron plus others
- By iron content
- By folic acid content

Control :

- No iron supplementation
- Placebo
- Same supplement without iron or folic acid

Outcomes:

Maternal

Critical

- Severe anaemia
- Maternal mortality
- Anaemia
- Haemoglobin concentrations
- Iron deficiency anaemia
- Iron deficiency
- Morbidity from malaria – incidence and severity (parasitaemia with or without symptoms)
- Adverse effects

Neonate/infant

Critical

- Anaemia
- Iron deficiency
- Iron deficiency anaemia
- Neural tube defects
- Low birth weight: less than 2500 g
- Birth weight
- Length at birth
- Cognitive performance
- Gestational age: less than 34 weeks versus less than 37 weeks versus no prematurity
- Mortality

Setting:

All settings

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